Case Report

Ipilimumab-Induced Hypophysitis May Not Affect All Pituitary Cell Lines: A Case Report

Anupam Kotwal, Sarika Rao, Richard Allen Haas

Abstract

Hypophysitis, a rare autoimmune condition, has now emerged as an adverse effect of ipilimumab (anti-cytotoxic T lymphocyte antigen 4 (CTLA4) mAb) therapy. The occurrence of ipilimumab-induced hypophysitis (IH) in studies has varied from 0% to 17%. This condition, because of secondary adrenal insufficiency, may be life-threatening if not recognized and managed promptly. Here we present a case of hypophysitis in the setting of ipilimumab therapy for malignant melanoma. The patient initially presented to his oncologist with a headache, diplopia, fatigue, nausea, hot flashes, anorexia and decreased libido shortly following the third cycle of ipilimumab. He was found to have pituitary enlargement with heterogeneous enhancement on magnetic resonance imaging (MRI). The initial diagnosis was based on clinical features, MRI findings and laboratory evidence of central hypogonadism and adrenal insufficiency. Other hormone levels were not tested that time and were only tested 5 months later when the patient did not tolerate the discontinuation of glucocorticoids. He continued to require glucocorticoid and testosterone replacement 14 months after the diagnosis. This case demonstrates IH causing anterior hypopituitarism leading to central hypoaldosteronism, central hypogonadism, reduced prolactin and possibly central hypothyroidism but preserved somatotroph function. Pituitary antibodies may be a possible method of detection of IH in addition to MRI and hormonal investigations. There is insufficient evidence to support the need to discontinue ipilimumab in the management of IH. Hypopituitarism due to IH may persist for several months or longer after ipilimumab is discontinued. This underlies the importance of continuous supplementation with all the hormones that are deficient as a consequence of hypopituitarism caused by IH.

Keywords: Ipilimumab; Hypophysitis; Hypopituitarism

Introduction

Autoimmune lymphocytic hypophysitis is the most common chronic inflammation to primarily affect the pituitary gland [1]. It has been divided into adenohypophysitis, infundibulohypophysitis, neurohypophysitis or panhypophysitis depending on the anatomical location involved, with adenohypophysitis being the most commonly reported. This rare condition has now emerged as an adverse effect of immune-modulatory therapy for malignancy. Cytotoxic T lymphocyte antigen 4 (CTLA4) is a key immune checkpoint molecule that downregulates T-cell activation and proliferation. It contributes to controlling autoimmunity, and in the presence of cancer, it limits the expansion of tumor-specific effector T cells, favoring cancer immune tolerance. Ipilimumab is an anti-CTLA4 monoclonal antibody which by blocking this molecule leads to enhanced T-cell activation and antitumor effects. It was approved by the US FDA in 2011 for treatment for metastatic or unresectable melanoma. The approved dose is 3 mg/kg administered as an intravenous infusion every 3 weeks for a total of four doses. Survival benefit has been demonstrated with 3 mg/kg [2], but not with lower doses. In some patients, maintenance therapy may continue with additional infusions at longer intervals. Multiple clinical trials have demonstrated improved survival in cancers especially malignant melanoma with ipilimumab therapy [2, 3]. Many of these trials have reported the occurrence of immune-related adverse effects (IRAEs) including endocrinopathies, colitis, dermatitis and hepatitis. Although the most commonly reported endocrinopathy is hypophysitis, rarely thyroiditis and occasionally adrenalitis [4-7] have been reported.

Ipilimumab-induced hypophysitis (IH), because of secondary adrenal insufficiency, may be life-threatening if not recognized and managed promptly [1]. Although a significant number of cases have been previously reported, there still remain major areas of uncertainty regarding the exact mechanism, risk factors, course and prognosis of this condition. Some studies have reported the cumulative dose of ipilimumab to
Table 1. Laboratory Investigations

<table>
<thead>
<tr>
<th>Laboratory investigations</th>
<th>Prior to ipilimumab</th>
<th>At diagnosis of IH</th>
<th>At 5-month follow-up</th>
<th>At 8-month follow-up</th>
<th>At 14-month follow-up</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total testosterone (ng/dL)</td>
<td>Not tested</td>
<td>11</td>
<td>&lt; 10</td>
<td>165</td>
<td>150</td>
<td>241 - 827</td>
</tr>
<tr>
<td>TSH (μIU/mL)</td>
<td>0.88</td>
<td>0.09</td>
<td>0.06</td>
<td>Not tested</td>
<td>0.09</td>
<td>0.28 - 3.89</td>
</tr>
<tr>
<td>Free T4 (ng/dL)</td>
<td>1.19</td>
<td>1.15</td>
<td>1.5</td>
<td>Not tested</td>
<td>0.83</td>
<td>0.58 - 1.64</td>
</tr>
<tr>
<td>Total T3 (ng/dL)</td>
<td>101</td>
<td>74</td>
<td>Not tested</td>
<td>Not tested</td>
<td>Not tested</td>
<td>97 - 178</td>
</tr>
<tr>
<td>AM Cortisol (μg/dL)</td>
<td>Not tested</td>
<td>0.09</td>
<td>1.4</td>
<td>Not tested</td>
<td>0.9</td>
<td>6.7 - 22.6</td>
</tr>
<tr>
<td>ACTH (pg/mL)</td>
<td>Not tested</td>
<td>Not tested</td>
<td>&lt; 5</td>
<td>Not tested</td>
<td>5</td>
<td>&lt; 46</td>
</tr>
<tr>
<td>ACTH stimulation test (μg/dL)</td>
<td>Not tested</td>
<td>Not tested</td>
<td>1.4, 9.2, 11.4</td>
<td>Not tested</td>
<td>Not tested</td>
<td>≥ 18</td>
</tr>
<tr>
<td>Prolactin (ng/mL)</td>
<td>Not tested</td>
<td>Not tested</td>
<td>0.6</td>
<td>Not tested</td>
<td>0.7</td>
<td>2.6 - 13.3</td>
</tr>
<tr>
<td>IGF-1 (ng/dL)</td>
<td>Not tested</td>
<td>Not tested</td>
<td>40</td>
<td>Not tested</td>
<td>Not tested</td>
<td>17 - 246</td>
</tr>
<tr>
<td>LH (mIU/mL)</td>
<td>Not tested</td>
<td>Not tested</td>
<td>1.4</td>
<td>Not tested</td>
<td>Not tested</td>
<td>1.2 - 8.6</td>
</tr>
<tr>
<td>Serum osmolality, urine osmolality and serum electrolytes</td>
<td>Within normal range</td>
<td>Within normal range</td>
<td>Within normal range</td>
<td>Within normal range</td>
<td>Within normal range</td>
<td></td>
</tr>
</tbody>
</table>
hypophysitis), confusion, memory loss, loss of libido, anosmia (less frequent than in classic lymphocytic autoimmune hypophysitis), headache, nausea, visual impairments such as diplopia. Affected individuals may present with nonspecific symptoms such as fatigue, weakness, headache, nausea, visual impairments such as diplopia (less frequent than in classic lymphocytic autoimmune hypophysitis), confusion, memory loss, loss of libido, anorexia, insomnia, hallucinations, temperature intolerance, and subjective sensation of fever and chills.

We present a patient with malignant melanoma who developed features of adenohypophysitis after the third cycle of ipilimumab therapy, and presented with pituitary mass effect as well as anterior hypopituitarism. Ipilimumab increases T-cell activity by blocking the inhibitory receptor CTLA4, leading to antitumor effects. However, the same mechanism might cause a spectrum of inflammatory side-effects classified as IRAEs. Autoimmunity has been proposed to be the mechanism responsible for these adverse effects. The occurrence of IH in studies has varied from 0% to 17% [2, 8, 10-15]; however, these studies have used different doses of ipilimumab ranging from 0.3 to 10 mg/kg. In a recent case series, 11% of patients undergoing treatment with ipilimumab developed hypophysitis [5]. Based on a review, there appears to be a dose-dependent increase in the occurrence of IH [10]. At the lower ipilimumab dose (1 - 3 mg/kg), it occurred in 1.8-3.3% of cases [8, 9]. When the dose exceeds 3 mg/kg, the occurrence of IH varies from 4.9 to 17% [13, 14]. Our patient developed symptoms after the third cycle of 3 mg/kg ipilimumab therapy for malignant melanoma. Most but not all cases of IH have been reported to occur after a similar duration of therapy. According to a review, patients who received 3 mg/kg ipilimumab developed symptoms at a median time of 11 weeks (that is, before the fourth dose), suggesting a possible cumulative effect [16]. This has also been supported by another recent review of clinical trials [4]. However, a study in which patients used 10 mg/kg ipilimumab reported that hypophysitis symptoms occurred after the first infusion (4 weeks) in one patient and after the fourth (16 weeks) in another [10], and a recent prospective cohort study did not find the cumulative dose of ipilimumab to be a risk factor for hypophysitis [5].

The clinical presentation of IH relates to pituitary mass effect and hormone deficiencies. Affected individuals may present with nonspecific symptoms such as fatigue, weakness, headache, nausea, visual impairments such as diplopia (less frequent than in classic lymphocytic autoimmune hypophysitis), confusion, memory loss, loss of libido, anorexia, insomnia, hallucinations, temperature intolerance, and subjective sensation of fever and chills. Earlier studies have reported that ACTH and TSH seem to be invariably lost, and most male patients have hypogonadotropic hypogonadism. Faje et al reported all cases with IH to have central hypothyroidism and hypogonadism; however, only approximately 50% of the affected individuals had secondary adrenal insufficiency [5]. The levels of IGF-1 were tested in only six of the 17 affected individuals and found to be low in one individual, and the prolactin level was found to be low in most of the affected individuals [5]. Faje et al did not report any cases of diabetes insipidus due to ipilimumab [5], and we could find only one case in the literature reporting this [10]. The pattern of loss of pituitary function from IH appears to be similar to classic autoimmune hypophysitis but different from other causes of anterior hypopituitarism. In most but not all cases of IH, MRI reveals enlargement of the pituitary gland (up to 60-100% of baseline size), with thickening of the stalk [5, 14]. In the case series by Min et al, only one out of eight patients had typical hypophysitis MRI findings, which resolved after 1 month [15]. The pituitary enlargement preceded the clinical diagnosis of hypophysitis in eight out of 17 IH patients, often by several weeks in the study by Faje et al [5]. The MRI findings in IH have been reported to be lesser in magnitude as compared to classic lymphocytic autoimmune hypophysitis [15]. Our patient was found to have pituitary enlargement with heterogeneous contrast enhancement at the time of initial diagnosis. The initial diagnosis was based on clinical features, MRI findings and laboratory evidence of adrenal insufficiency and hypogonadism by the patient’s oncologist. Other hormone levels were not tested at that time and were only tested later when the patient did not tolerate the discontinuation of glucocorticoids. He then demonstrated soft tissue fullness of the pituitary with heterogeneous enhancement after contrast.

Discussion}

The clinical presentation of IH relates to pituitary mass effect and hormone deficiencies. Affected individuals may present with nonspecific symptoms such as fatigue, weakness, headache, nausea, visual impairments such as diplopia (less frequent than in classic lymphocytic autoimmune hypophysitis), confusion, memory loss, loss of libido, anorexia, insomnia, hallucinations, temperature intolerance, and subjective sensation of fever and chills. Earlier studies have reported that ACTH and TSH seem to be invariably lost, and most male patients have hypogonadotropic hypogonadism. Faje et al reported all cases with IH to have central hypothyroidism and hypogonadism; however, only approximately 50% of the affected individuals had secondary adrenal insufficiency [5]. The levels of IGF-1 were tested in only six of the 17 affected individuals and found to be low in one individual, and the prolactin level was found to be low in most of the affected individuals [5]. Faje et al did not report any cases of diabetes insipidus due to ipilimumab [5], and we could find only one case in the literature reporting this [10]. The pattern of loss of pituitary function from IH appears to be similar to classic autoimmune hypophysitis but different from other causes of anterior hypopituitarism. In most but not all cases of IH, MRI reveals enlargement of the pituitary gland (up to 60-100% of baseline size), with thickening of the stalk [5, 14]. In the case series by Min et al, only one out of eight patients had typical hypophysitis MRI findings, which resolved after 1 month [15]. The pituitary enlargement preceded the clinical diagnosis of hypophysitis in eight out of 17 IH patients, often by several weeks in the study by Faje et al [5]. The MRI findings in IH have been reported to be lesser in magnitude as compared to classic lymphocytic autoimmune hypophysitis [15]. Our patient was found to have pituitary enlargement with heterogeneous contrast enhancement at the time of initial diagnosis. The initial diagnosis was based on clinical features, MRI findings and laboratory evidence of adrenal insufficiency and hypogonadism by the patient’s oncologist. Other hormone levels were not tested at that time and were only tested later when the patient did not tolerate the discontinuation of glucocorticoids. He then demonstrated soft tissue fullness of the pituitary with heterogeneous enhancement after contrast.
After re-initiation of slightly higher than physiologic hydrocortisone and testosterone replacement [14]. In our patient, with 4–26 months follow-up and some continued to require glucocorticoids with ipilimumab, regardless of management, all patients with IH [5]. In the largest clinical trial of 163 patients treated with ipilimumab (anti-CTLA4 mAb), the development of antibodies against corticotrophs, thyrotrophs and gonadotrophs in patients with IH [20]. This might explain an underlying mechanism for the autoimmune hypophysitis caused by ipilimumab. However, the exact antigenic target(s) for this condition remains to be elucidated. In any patient with malignancy treated with ipilimumab who develops features concerning for hypophysitis, metastasis to the pituitary should be considered, especially if the pituitary enlargement does not respond to glucocorticoid therapy [4].

Conclusions

Autoimmune hypophysitis has emerged as an IRAE of ipilimumab (anti-CTLA4 mAb). The clinical presentation of IH relates to pituitary mass effect and hypopituitarism. It usually affects the anterior pituitary, most commonly involved cell lines being corticotrophs, thyrotrophs and gonadotrophs, with lesser-reported involvement of somatotrophs. Prolactin may be elevated or reduced and posterior pituitary is usually spared. Pituitary antibodies might be a possible method of detection in addition to hormonal and radiological investigations; however, the antigenic target remains to be elucidated. There is insufficient evidence to support the need for discontinuing ipilimumab or the superiority of initial high-dose glucocorticoids versus physiologic hormone replacement in the management of IH. Most clinical and radiological features of IH are consistent with classic lymphocytic hypophysitis; however, the aspects in which these differ are male preponderance, increased incidence in older age and lesser magnitude of MRI findings reported with IH. Pituitary function should be tested before starting ipilimumab, and when IH is suspected, it should be managed promptly as the resulting adrenal insufficiency may be life-threatening. Failure of resolution of pituitary enlargement should raise the concern for metastasis of the primary malignancy to the pituitary. Hypopituitarism due to IH usually persists for several months or longer after diagnosis even though pituitary mass effect resolves after glucocorticoid therapy. This underlines the importance of continuous replacement
of the deficient hormones, unless there is evidence of recovery of pituitary function.

Conflict of Interest

The authors have no conflicts of interest.

Abbreviations

CTLA4: cytotoxic T lymphocyte antigen 4; IRAEs: immune-related adverse effects; IH: ipilimumab-induced hypophysitis; MRI: magnetic resonance imaging

References